



**University of
Zurich^{UZH}**

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2011

Iron sucrose with and without recombinant erythropoietin for the treatment of severe postpartum anemia: A prospective, randomized, open-label study

Krafft, A ; Breymann, C

Abstract: Aim: Postpartum anemia is a common problem in obstetrics. Depending on the severity of anemia, it can cause a wide range of symptoms. Obstetrical management should be focused on avoiding blood transfusion in young and otherwise healthy women. The aim of this study was to examine the effectiveness of recombinant human erythropoietin (rhEPO) combined with iron sucrose compared to iron sucrose alone in patients with severe postpartum anemia. Methods: A prospective randomized study was conducted in women with severe postpartum anemia (Hb < 8.5 g/dL). The first group received 200 mg iron sucrose intravenously daily on days 1-4. The second group received 200 mg iron sucrose plus 10.000E rhEPO in the same regimen. Twenty women were enrolled in each group. The follow-up period was two weeks. Results: Baseline Hb was 7.1 g/dL and 7.5 g/dL, respectively, depending on the subgroup. Hemoglobin values increased close to normal values within two weeks in both groups treated with iron sucrose alone or in combination with rhEPO (10.5 g/dL, 10.7 g/dL, respectively). Conclusion: In general, iron sucrose alone is a sufficient anemia therapy agent. A subgroup of patients (i.e. with a more pronounced inflammatory response after cesarean section) may benefit from additional rhEPO therapy. Despite being severely anemic, none of our patients required transfusion. Iron sucrose as well as rhEPO was very well tolerated. The benefit of the therapy lies in the avoidance of allogenic blood transfusions with their potential side effects. In cases of severe anemia after operative delivery, additional rhEPO therapy can result in a faster Hb increase and, therefore, faster recovery.

DOI: <https://doi.org/10.1111/j.1447-0756.2010.01328.x>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-42864>

Journal Article

Accepted Version

Originally published at:

Krafft, A; Breymann, C (2011). Iron sucrose with and without recombinant erythropoietin for the treatment of severe postpartum anemia: A prospective, randomized, open-label study. *Journal of Obstetrics and Gynaecology Research*, 37(2):119-124.

DOI: <https://doi.org/10.1111/j.1447-0756.2010.01328.x>



Iron sucrose with and without recombinant erythropoietin for the treatment of severe postpartum anemia. A prospective, randomized, open-label study.

Journal:	<i>The Journal of Obstetrics and Gynaecology Research</i>
Manuscript ID:	JOGR-2009-0640.R2
Manuscript Type:	Original Manuscript
Date Submitted by the Author:	22-Jan-2010
Complete List of Authors:	Krafft, Alexander; University Hospital Zurich, Obstetrics and Gynecology Breyman, Christian; University Hospital Zurich, Department of Obstetrics and Gynecology
Keywords:	2.718 Post Partum Hemorrhage < 2.700 Obstetrics: Diagnosis and Management < 2 Obstetrics, 2.711 Cesarean Section < 2.700 Obstetrics: Diagnosis and Management < 2 Obstetrics



Iron sucrose with and without recombinant erythropoietin for the treatment
of severe postpartum anemia. [A prospective, randomized, open-label
study.](#)

Alexander Krafft, Christian Breymann

Feto-maternal Hematology Group, Division of Obstetrics, Department of
Obstetrics and Gynecology, University Hospital Zurich

Corresponding author and reprint requests:

Alexander Krafft, M.D.

Division of Obstetrics

Department of Obstetrics and Gynecology

University Hospital Zurich

CH 8091 Zurich, Switzerland

Tel: +41 44 255 5148

Fax: +41 44 255 4430

E mail: alexander.krafft@usz.ch

Running Head: Treatment of severe postpartum anemia.

Abstract

Aim: Postpartum anemia is a common problem in obstetrics. Depending on the severity of anemia, it can cause a wide range of symptoms. Obstetrical management should be focused on avoiding blood transfusion in young and otherwise healthy women. Aim of this study was to examine the effectiveness of rhEPO combined with iron sucrose compared to iron sucrose alone in patients with severe postpartum anemia.

Methods: Prospective randomized study in women with severe postpartum anemia (Hb < 8.5 g/dL). Group one received 200mg iron sucrose intravenously daily on days 1-4. The second group received 200mg iron sucrose plus 10.000E rhEPO in the same regimen. 20 women were enrolled in each group. Follow-up was two weeks.

Results: Baseline Hb was 7.1 g/dL and 7.5 g/dL respectively depending on the subgroup. Hemoglobin values increased close to normal values within two weeks in both groups treated with iron sucrose alone or in combination with rhEPO (10.5 g/dL, 10.7 g/dL, respectively).

Conclusions: In general, iron sucrose alone is a sufficient anemia therapy agent. A subgroup of patients (i.e. with a more pronounced inflammatory response after caesarean section) may benefit from additional rhEPO therapy. Despite being severely anemic, none of our patients required transfusion. Iron sucrose as well as rhEPO was very well tolerated. The benefit of the therapy lies in the avoidance of allogenic blood transfusions with their potential side effects. In cases of severe anemia after operative delivery additional rhEPO therapy can result in a faster Hb increase and therefore faster recovery.

Key words: anemia, iron-deficiency, iron-sucrose, postpartum, recombinant EPO

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Introduction

Postpartum anemia is a common problem in obstetrics. Depending on the grade of anemia, symptoms like reduced exercise performance, tiredness, headache, increased cardiovascular strain, higher risk for infections, and lactation problems occur. As in other specialties, anemia often results in a longer stay in hospital.¹ According to WHO criteria severe anemia is defined by a hemoglobin value < 8.5 g/dL.^{2,3}

The known risks of allogenic blood transfusions for treatment of severe anemia, as transmission of pathogens (i.e. Hepatitis B/C, HIV, and CMV), alloimmunization and immunosuppression, led to the search for alternative therapeutic options.^{4,5}

Several studies in have shown the superiority of IV iron over oral iron in the treatment of postpartum anemia. IV iron not only corrects anemia faster, but is also second to none in replenishing iron stores.⁶⁻⁸

Recombinant human erythropoietin (rhEPO) is successfully used since the mid 1980's for treatment of renal anemia. RhEPO is not only well established in the treatment of anemia under chemotherapy, anemia of chronic disease, perioperative correction of anemia or autologous blood donation⁹⁻¹¹ but as well in the correction of anemia in pregnancy and postpartum.¹²⁻¹⁵

Elevation of inflammation mediators in chronic or inflammatory disease interferes with iron utilization.¹⁶ With the discovery of hepcidin as a key regulator of iron absorption and distribution a major step has been made in the understanding of iron metabolism and pathogenesis of anemia of inflammation.¹⁷ Studies showed a connection between elevated cytokine levels (TNF alpha, IL1) and inadequate erythropoietin response.¹⁸ Similar to the

changes observed in anemia of chronic disease, even minor surgical procedures as well as vaginal delivery already lead to a rise in cytokine levels, which are possibly responsible for suppressed erythropoiesis.^{19,20} Different studies showed the effectiveness of rhEPO in insufficient erythropoiesis due to inadequate endogenous erythropoietin levels.^{21,22} Admittedly, Wagstrom et al. showed that iv iron alone might be sufficient in treating severe postpartum anemia.¹⁵

The main handicap of rhEPO therapy is its high cost. Therefore, aim of this study was to examine the effectiveness of IV iron sucrose with and without the combination of rhEPO in the treatment of postpartum anemia and if there are, to define patients who profit from additional rhEPO therapy. In contrast to previous studies²²⁻²⁴ we selected only patients with severe postpartum anemia (Hb < 8.5

g/dL). As in earlier studies, we opted to use an amount of iron (800 mg) which should be sufficient to treat the grade of anemia and to restore iron stores sufficiently. Furthermore, as we tried to establish a therapy scheme ready for routine use, our aim was to simplify this scheme as much as possible. The same holds true for the chosen rhEPO dosage. 10.000 U rhEPO daily reflects a mean dosage of 150 U / kg bodyweight, which is a commonly used medium rhEPO dose.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Material and Methods

In this prospective, randomized single-center study 40 postpartum women with severe anemia (Hb < 8.5 g/dL) were included.

The inclusion criteria were prepartal hemoglobin > 10.0 g/dL, severe postpartum anemia, defined by a hemoglobin < 8.5 g/dL 24 – 48 h after delivery. Exclusion criteria were any hematological, chronic-inflammatory or malignant disease, cardiac or renal dysfunction, hemosiderosis, history of iron intolerance, peripartal blood transfusion.

Patients were randomized using sealed envelopes containing numbers allocated to one of two groups.

All women gave informed consent and the study was approved by the hospital ethics committee which is a division of the cantonal ethics committee in Zurich.

Treatment

Treatment was started between 24 and 48 hours after delivery and administered daily on 4 subsequent days.

Group I (n=20): iron sucrose (Venofer[®], Vifor, St.Gallen, Switzerland), 200 mg (=10 mL) via intravenous (i.v.) catheter daily on days 1-4 ([no rhEPO placebo was used](#));

Group II (n=20): rhEPO (Eprex[®], Janssen-Cilag, Baar, Switzerland) (10.000 U daily) via i.v. catheter on days 1-4 plus iron sucrose (identical as in group I).

All treatments were administered at room temperature. The iron sucrose complex was administered first and was diluted in 250 mL 0.9 % sodium chloride, followed by 5 mL saline to flush iron particles from the tubing. Where applicable, rhEPO followed as a bolus, again followed by 5 mL saline.

The study was conducted over a 24 months period between 2004 and 2006.

Laboratory investigations

Blood samples were taken before, and 4, 7 and 14 days after start of therapy. On day 4, blood samples were taken before administering medication intravenously.

Hematocrit, hemoglobin, red cell indices (mean corpuscular volume, MCV; mean corpuscular hemoglobin, MCH; mean corpuscular hemoglobin concentration, MCHC), percentage of hypochromic red cells, and

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

reticulocyte count were determined using Advia[®] analyzer (Bayer[®] Diagnostics, Leverkusen, Germany). Measures of iron status were serum ferritin, obtained by immunochemiluminescence (Elecsys[®] Systems, Roche AG, Switzerland), transferrin saturation and soluble transferrin receptor concentration, measured by enzyme immunoassay based upon the double antibody sandwich method (Ramco Laboratories, Houston, Texas, USA). C-reactive protein (CRP) was determined by immunoprecipitation, folic acid concentration in erythrocytes, and vitamin B12 and erythropoietin levels by radioimmunoassay. Interleukin 6 was measured using chemiluminescence- enzyme immunoassay.

Statistical analysis

Groups were compared using the Mann-Whitney test. Based on the hemoglobin increase on day 15, post-hoc power calculation revealed a power of 0.87. A significance level of $p < 0.05$ was used in all tests. Statistics were calculated using Statview[®] software (SAS Institute Inc., Cary, NC, USA).

Results

Patients characteristics

40 women were included. Mean gestational age at delivery was 38 weeks (24–42 weeks). Delivery was spontaneous in 19 of cases, vaginal operative in 8, and via caesarean section in 13 cases. Estimated blood loss was 838 ± 600 mL (250–2150 mL). Reasons for hemorrhage were: retention of placenta (8), placental abruption (5), atonic bleeding (3), fibroids (2) and placenta previa (1). The remaining women delivered without any further complications apart from anemia.

Baseline data

Mean *prepartal* hemoglobin was 11.5 ± 1.1 g/dL (range 10.0 – 15.1 g/dL), and mean *postpartum* hemoglobin was 7.3 ± 0.9 g/dL (5.0 – 8.4 g/dL) [mean hematocrit 22.2 ± 2.8 %, (16.0 – 26.7%)]. Mean postpartum (=baseline) ferritin was 38 ± 55 µg/L (median 24; 2 – 312 µg/L).

At baseline vitamin B12 and folic acid levels were within the normal range, except one patient with a vitamin B12 value of 121 ng/L, which is below the lower limit of 180 ng/L. There were no statistically significant differences between the two groups in baseline data.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Erythropoietic response

In the overall population the mean hemoglobin increase one week after start of treatment was 2.1 ± 0.1 g/dL ($0.6 - 3.9$ g/dL) (Δ Hct 7.2 ± 0.4 %; $3.4 - 12.9$ %), after two weeks 3.3 ± 0.1 g/dL ($1.6 - 4.8$ g/dL) (Δ Hct 10.9 ± 0.3 %; $6.0 - 16.1$ %). Absolute hemoglobin values one and two weeks after start of therapy were 9.4 ± 0.2 g/dL ($7.0 - 11.9$ g/dL) and 10.6 ± 0.1 g/dL ($8.6 - 12.6$ g/dL), respectively (hematocrit: 29.5 ± 0.6 %; $20.9 - 36.9$ after one week and 33.1 ± 0.4 %; $27.2 - 38.9$ after two weeks) (Fig. 1).

Subgroup values for baseline and end of treatment are shown in table 1.

From day 4 after start of treatment the difference between the hemoglobin increase was statistically significant between group I (iron sucrose alone) and group II (iron sucrose + rhEPO) (day 4: $0.5 (\pm 0.1)$ g/dL vs. $1.0 (\pm 0.2)$ g/dL; $p < 0.05$; day 8: $1.9 (\pm 0.1)$ g/dL vs. $2.4 (\pm 0.2)$ g/dL; $p < 0.05$; day 15: $3.0 (\pm 0.1)$ g/dL vs. $3.9 (\pm 0.1)$ g/dL; $p < 0.05$).

Reticulocytes showed an increase from baseline in both groups until day 8 and returned to values comparable to baseline data on day 15. Reticulocytosis was statistically significantly higher in the group treated with iron and rhEPO (Fig. 2a).

Endogenous EPO (eEPO) levels at baseline were elevated in all patients with no statistically significant difference in both groups (mean 154 U/L ± 21 , range $33 - 589$ U/L). After the end of treatment endogenous EPO levels decreased continuously to day 15 with no statistically significant difference in both groups (overall mean 29 U/L, ± 2 , range $8 - 69$ U/L).

There was no correlation between the grade of anemia and eEPO prior to therapy (Hb $p = 0.07$, $r^2 = 0.087$; Hct $p = 0.12$, $r^2 = 0.065$).

Iron status

Baseline and end of study data are shown in table 1. Highest ferritin levels were measured on day 4 [mean 453 $\mu\text{g/L}$, median 443 (211 – 863 $\mu\text{g/L}$)], decreasing continuously to day 15 [mean 206 $\mu\text{g/L}$, median 187 (88 – 461 $\mu\text{g/L}$)]. There was no statistically significant difference between both groups throughout the study period.

Hypochromic erythrocytes increased in both groups during the study period. Percentage of hypochromic erythrocytes was statistically significantly higher in the rhEPO group than in the group treated with iron alone on days 8 and 15 (Fig. 2b).

Soluble transferrin receptor (sTfR) levels were elevated in both groups at baseline and increased further throughout the study period. On day 8 sTfR levels in the rhEPO group were statistically significantly higher than in the iron alone treated group (Fig. 2c).

Inflammatory reaction

CRP levels were elevated at baseline in all patients (mean 57 ± 6 mg/L) but almost normalized by day 15 (mean 6 ± 1 mg/L). There was no statistically significant difference between both groups.

Baseline Interleukin 6 (IL-6) levels were elevated in all patients (mean 18 ± 3 ng/L) and almost normalized by the end of the study period (mean 5 ± 0.3 ng/L) with no statistically significant difference between both groups whatsoever.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Patient subgroups

To identify patients at greatest potential benefit from additional rhEPO therapy we performed a subgroup analysis according to the mode of delivery.

At comparison of women who underwent caesarean section (n = 13), the increase in hemoglobin levels was statistically significantly higher in the subgroup treated with additional rhEPO (n = 6) compared to women receiving IV iron alone (n = 7). Women after caesarean section showed statistically significantly lower eEPO levels but statistically significantly higher IL-6 levels compared to women who gave birth spontaneously or had a vaginal operative delivery (n = 27).

Safety

Assessment of vital signs was comparable between the groups throughout the study. There were no serious adverse reactions to rhEPO or iron sucrose. There was no hypo- or hypertensive response during therapy. No thromboembolic complications were seen. Minor side-effects were metallic taste in 12 patients, and 3 patients reported warm flush over a few minutes. Treatment was well tolerated overall in terms of both clinical and patient self-evaluation. No patient needed blood transfusion in addition to therapy.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Discussion

In conclusion intravenous iron sucrose is effective and safe in treating severe anemia in a postpartum population. Additional rhEPO could be indicated for patients especially after operative delivery with serious anemia related symptoms or refusing transfusions in which case rhEPO represents the most effective therapy alternative.

In this study we were able to show a marked increase of hemoglobin and hematocrit values close to normal within two weeks in both groups treated with iron sucrose alone or in combination with rhEPO. Despite being severely anemic, none of our patients required transfusion. The benefit of the therapy clearly lies in the avoidance of allogenic blood transfusions with their potential side effects, such as infection or alloimmunization.⁴ Depending on the severity of anemia, patients suffer from increased cardiovascular strain, autonomous dysregulation, reduced exercise performance and various symptoms such as tiredness and dizziness. Furthermore it negatively affects the course of the puerperium, the ability to breastfeed and duration of hospitalization.^{23,25}

Already one week after start of treatment, patients in group II had a statistically significant higher increase in hemoglobin levels than patients treated with iron alone (group I). This is in contrast to the study of Wagstrom et al who examined a similar protocol in women with a comparable grade of postpartum anemia.¹⁵ The main differences to our study are a lower total iron dose, a lower rhEPO dose, or a longer interval between rhEPO applications respectively. We agree with Wagstrom and colleagues that intravenous iron alone is sufficient in treating severe

postpartum anemia but identified a subgroup which profits from additional rhEPO therapy. Our data obtained from patients after cesarean section show statistically significant higher IL-6 levels and statistically significant lower eEPO levels, whereas baseline hemoglobin levels are the same compared to patients after vaginal delivery. After delivery inflammatory mediators are released, which are causing suppressed erythropoiesis and alteration of iron metabolism in postpartum anemia.^{19 20} Cytokine release leads to increased iron absorption in macrophages and the reticulo-endothelial system.²⁰ It is suggested, that these cytokine triggered processes also influence anemia of chronic, rheumatoid or inflammatory disease.²⁶ In the postoperative situation inflammatory mediators seem to be increased in comparison to spontaneous delivery.

We believe, in patients after operative delivery combined therapy with iron sucrose and rhEPO is beneficial.

In our study there was no correlation between the grade of anemia and eEPO levels as suggested by Cazzola et al.²¹ This circumstance might be explained by cytokine activation as described above.

Additional rhEPO therapy leads to a statistically significant increase of reticulocytes by day 8 in the rhEPO treated group, but despite IV iron supplementation aggravates functional iron deficiency shown by a higher percentage of hypochromic red cells and higher sTfR levels (Fig. 2a-c). However, together with postpartum reduction of maternal total red cell mass, decline of pregnancy-induced hydremia, reduced iron loss due to postpartum amenorrhea, the substituted amount of iron should be sufficient not only to correct anemia but also to restore body iron stores.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Intravenous iron administration is safe, especially if iron sucrose is used. Hoigné et al. published adverse event profiles of 4 different databases (8100 patients) and calculated a adverse event rate of 0.36% with not a single life threatening event.²⁷ RhEPO therapy is usually well tolerated as well, adverse events, such as hypertension are described mainly in patients with chronic renal failure.²⁸ As millions of anemic patients with a variety of indications have been treated with different epoetin preparations, some years ago cases of epoetin-associated pure red cell aplasia (PRCA) have been identified and raised questions on safety of the drug.²⁹ As these cases occurred in hemodialysis patients who received epoetins subcutaneously for several months we believe PRCA is not an issue in the short-term treatment setting, particularly if rhEPO is given intravenously.

Acknowledgements

None.

The authors declare no conflict of interest.

For Peer Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. Dunne JR, Malone D, Tracy JK, *et al.* Perioperative anemia: an independent risk factor for infection, mortality, and resource utilization in surgery. *J Surg Res* 2002;**102**: 237-44.

2. Dowdle W. CDC Criteria for anemia in children and childbearing-aged women. *Morb Mortal Wkly Rep* 1989;**38**: 400-4.

3. Huch R, Huch A. Erythropoietin in obstetrics. *Hematol Oncol Clin North Am* 1994;**8**: 1021-40.

4. Lefevre P, Poullin P. Current information on risks of allogenic blood transfusion TAB - The NATA Textbook. *Transfusion Medicine and Alternatives in Transfusion Medicine*, 2000:60-6.

5. Williamson L, Lowe S, Lowe E, *et al.* Serious hazards of transfusion (SHOT) initiative: analysis of the first two annual reports. *Br Med J* 1999;**319**: 16-9.

6. Bhandal N, Russell R. Intravenous versus oral iron therapy for postpartum anaemia. *Bjog* 2006;**113**: 1248-52.

7. Van Wyck DB, Martens MG, Seid MH, *et al.* Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial. *Obstet Gynecol* 2007;**110**: 267-78.

8. Westad S, Backe B, Salvesen KA, *et al.* A 12-week randomised study comparing intravenous iron sucrose versus oral ferrous sulphate for treatment of postpartum anemia. *Acta Obstet Gynecol Scand* 2008;**87**: 916-23.

9. Rohling R, Zimmermann A, Breymann C. Intravenous versus oral iron supplementation for preoperative stimulation of hemoglobin synthesis using recombinant human erythropoietin. *J Hematother Stem Cell Res* 2000;**9**: 497-500.

10. Rizzo JD, Somerfield MR, Hagerty KL, *et al.* Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. *J Clin Oncol* 2008;**26**: 132-49.
11. Alghamdi AA, Albanna MJ, Guru V, Brister SJ. Does the use of erythropoietin reduce the risk of exposure to allogeneic blood transfusion in cardiac surgery? A systematic review and meta-analysis. *J Card Surg* 2006;**21**: 320-6.
12. Breymann C, Visca E, Huch R, Huch A. Efficacy and safety of intravenously administered iron sucrose with and without adjuvant recombinant human erythropoietin for the treatment of resistant iron-deficiency anemia during pregnancy. *Am J Obstet Gynecol* 2001;**184**: 662-7.
13. Hatzis T, Cardamakis E, Tsapanos V, *et al.* The effects of recombinant human erythropoietin given immediately after delivery to women with anaemia. *Curr Med Res Opin* 2003;**19**: 346-9.
14. Bencaiova G, Krafft A, Burkhardt T, Breymann C. Variable efficacy of recombinant human erythropoietin in anemic pregnant women with different forms of heterozygous hemoglobinopathy. *Acta Haematol* 2006;**116**: 259-65.
15. Wagstrom E, Akesson A, Van Rooijen M, *et al.* Erythropoietin and intravenous iron therapy in postpartum anaemia. *Acta Obstet Gynecol Scand* 2007;**86**: 957-62.
16. Jongen-Lavrencic M, Peeters HR, Vreugdenhil G, Swaak AJ. Interaction of inflammatory cytokines and erythropoietin in iron metabolism and erythropoiesis in anaemia of chronic disease. *Clin Rheumatol* 1995;**14**: 519-25.
17. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood* 2003;**102**: 783-8.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

18. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005;**352**: 1011-23.

19. Breymann C, Perewusnyk G, Guntermann H, *et al.* Unrecognised iron deficiency in critical illness. *Lancet* 1999;**353**: 841-2.

20. van Iperen CE, Kraaijenhagen RJ, Biesma DH, *et al.* Iron metabolism and erythropoiesis after surgery. *Br J Surg* 1998;**85**: 41-5.

21. Cazzola M, Mercuriali F, Brugnara C. Use of recombinant human erythropoietin outside the setting of uremia. *Blood* 1997;**89**: 4248-67.

22. Breymann C, Richter C, Hüttner C, *et al.* Effectiveness of recombinant erythropoietin and iron sucrose vs. iron therapy only, in patients with postpartum anaemia and blunted erythropoiesis. *Eur J Clin Invest* 2000;**30**: 154-61.

23. Huch A, Eichhorn KH, Danko J, *et al.* Recombinant human erythropoietin in the treatment of postpartum anemia. *Obstet Gynecol* 1992;**80**: 127-31.

24. Breymann C, Zimmermann R, Huch R, Huch A. Use of recombinant human erythropoietin in combination with parenteral iron in the treatment of postpartum anaemia. *Eur J Clin Invest* 1996;**26**: 123-30.

25. Broche DE, Gay C, Armand-Branger S, *et al.* [Acute postpartum anaemia. Clinical practice and interest of intravenous iron]. *Gynecol Obstet Fertil* 2004;**32**: 613-9.

26. Cazzola M, Ponchio L, de Benedetti F, *et al.* Defective iron supply for erythropoiesis and adequate endogenous erythropoietin production in the anemia associated with systemic-onset juvenile chronic arthritis. *Blood* 1996;**87**: 4824-30.

27. Hoigné R, Breymann C, Künzi U, Brunner F. Parenteral iron therapy: problems and possible solutions. *Schweiz Med Wochenschr.* 1998;**128**: 528-35.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
28. Singbartl G. Adverse events of erythropoietin in long-term and in acute/short-term treatment. Clin Investig 1994;**72**: S36-43.
29. McKoy JM, Stonecash RE, Cournoyer D, *et al.* Epoetin-associated pure red cell aplasia: past, present, and future considerations. Transfusion 2008;**48**: 1754-62.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure Legends

Figure 1. Erythropoietic response. Increase of hemoglobin versus day 0 in patients receiving iron sucrose alone (red line) or iron sucrose plus rhEPO (blue line). *Asterisk*, $P < .05$.

Figure 2. Reticulocyte count **(a)**, Hypochromic red blood cell count **(b)**, soluble transferrin receptor concentration **(c)** in patients receiving iron sucrose alone (red line) or iron sucrose plus rhEPO (blue line). *Asterisk*, $P < .05$.

For Peer Review

Table 1: Baseline and end of treatment data for groups I and II (Data are given as mean \pm SD)

		Group I	Group II	p	
		(iv iron)	(iv iron +rhEPO)		
		n=20	n=20		
Hemoglobin (g/dL)	Baseline	7.5 \pm 0.7	7.1 \pm 1.1	ns	Deleted: .3
	End of Treatment	10.5 \pm 0.7	10.7 \pm 1.2	ns	Deleted: .2
Hematocrit (%)	Baseline	22.8 \pm 2.2	21.4 \pm 3.3	ns	Deleted: .2
	End of Treatment	32.9 \pm 1.9	33.4 \pm 3.5	ns	Deleted: .1
Reticulocytes (%)	Baseline	3.0 \pm 0.8	3.8 \pm 1.8	ns	Deleted: 8.7
	End of Treatment	3.7 \pm 1.3	3.9 \pm 1.6	ns	Deleted: .3
Endogenous EPO (U/L)	Baseline	128 \pm 74	184 \pm 173	ns	Deleted: .3
	End of Treatment	29 \pm 15	30 \pm 16	ns	Deleted: .0
Ferritin (μ g/L)	Baseline	32 \pm 37	46 \pm 73	ns	Deleted: .3
	End of Treatment	221 \pm 102	187 \pm 89	ns	Deleted: .5
Soluble Transferrin-receptor (μ g/ml)	Baseline	5 \pm 3	6 \pm 8	ns	Deleted: .4
	End of Treatment	11 \pm 3	12 \pm 3	ns	Deleted: .0
C-reactive protein (mg/L)	Baseline	56 \pm 36	57 \pm 38	ns	Deleted: .4
	End of Treatment	8 \pm 7	4 \pm 3	ns	Deleted: 7.6
Interleukin 6 (ng/L)	Baseline	21 \pm 26	14 \pm 12	ns	Deleted: .0
	End of Treatment	5 \pm 1	5 \pm 2	ns	Deleted: .2
Vit. B12 (ng/L)	Baseline	298 \pm 142	257 \pm 86	ns	Deleted: .2
Blood loss (mL)	Baseline	817 \pm 579	864 \pm 643	ns	Deleted: 4.7

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

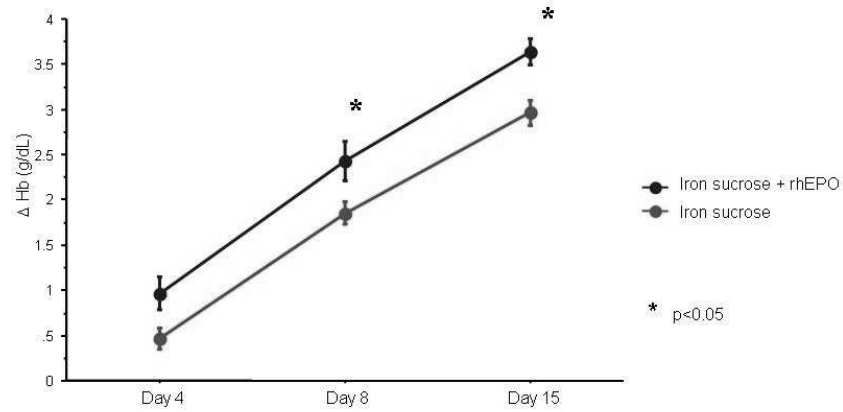


Fig. 1
254x190mm (96 x 96 DPI)

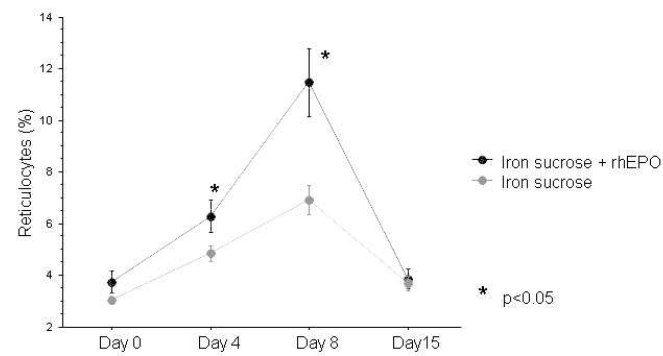


Fig. 2a
254x190mm (96 x 96 DPI)

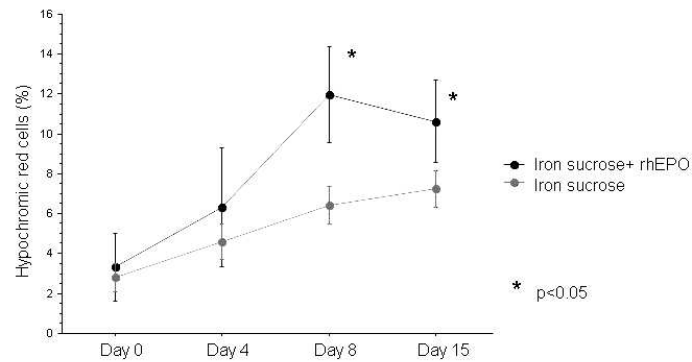


Fig. 2b
254x190mm (96 x 96 DPI)

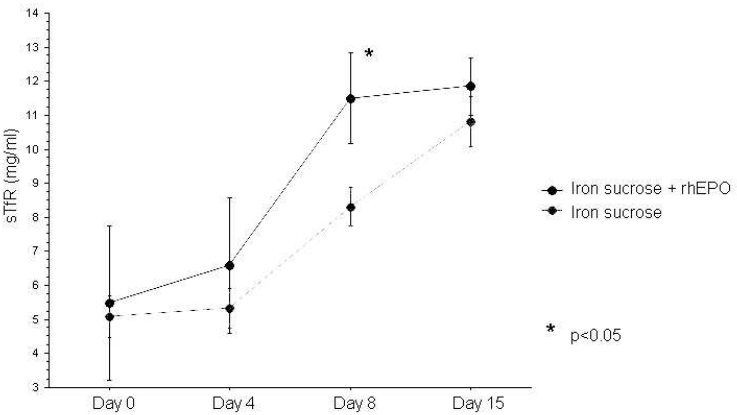


Fig. 2c
254x190mm (96 x 96 DPI)